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Toward the Synthesis of Didemnaketal B: A Convergent Synthesis of the C9−C28 Subunit

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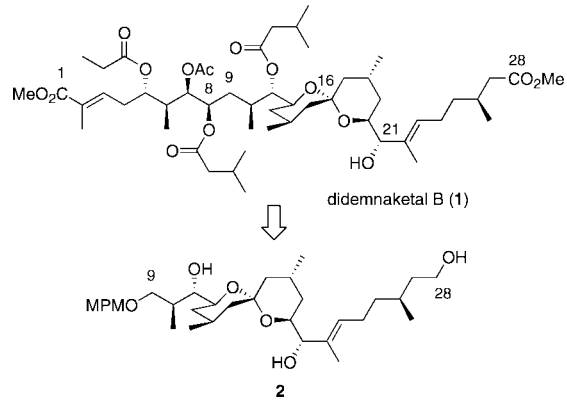
ABSTRACT



Synthesis of the C9−C28 subunit of didemnaketal B has been developed. This subunit was convergently prepared from four chiral synthons and at the longest linear sequence required 16 steps.

Didemnaketal B (**1**), which has been recognized as a potent inhibitor of the HIV-protease, was isolated from ascidian of the genus *Didemnum* by Faulkner and co-workers.[1] The planer structure of didemnaketal B was first disclosed in 1991,[1] and the stereochemical properties, including an absolute configuration, were derived from a combination of spectroscopic and degradative studies.[2] Aside from biological activity, didemnaketal B contains a number of intriguing structural features such as a spiroketal moiety and two side chains with eight chiral centers. These structural and biological properties have brought interest to synthetic organic chemists. Although many of the efforts for the synthesis of didemnaketal B and related compounds have been reported,[3,4] a total synthesis has not yet been reported. Recently, we reported on a model study for the construction of a spiroketal moiety through an enantioselective direct aldol reaction using a chiral dinuclear zinc catalyst.[5] In this communication, we report our studies that have led to a synthesis of the C9−C28 subunit **2** containing the spiroketal moiety through a highly convergent strategy.

A highly convergent synthetic plan for **2** is shown in Scheme 1. Subunit **2** would be accomplished by the addition

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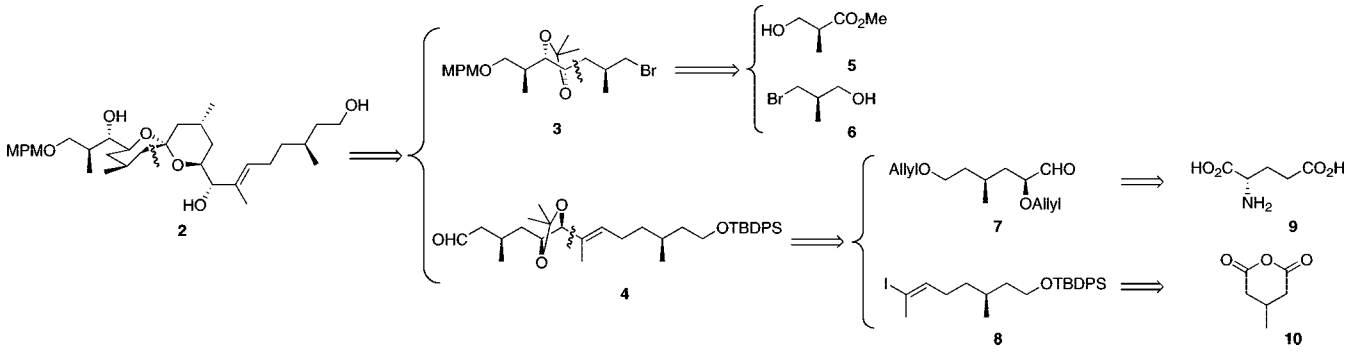
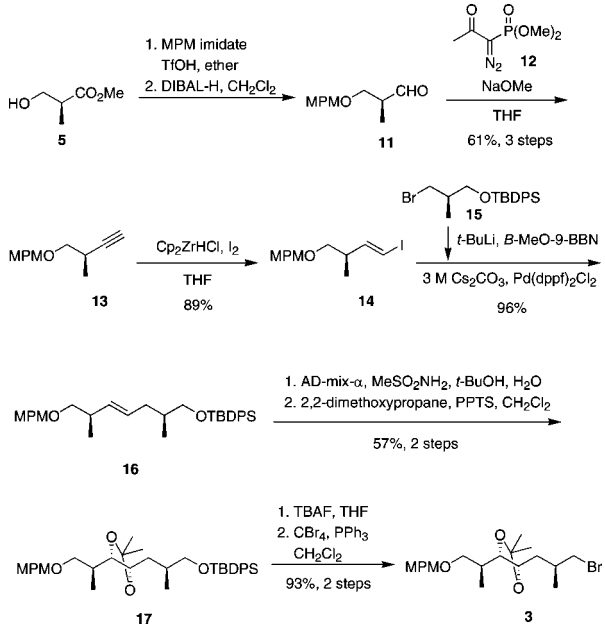
Scheme 1. Synthetic Plan of the C9−C28 Subunit



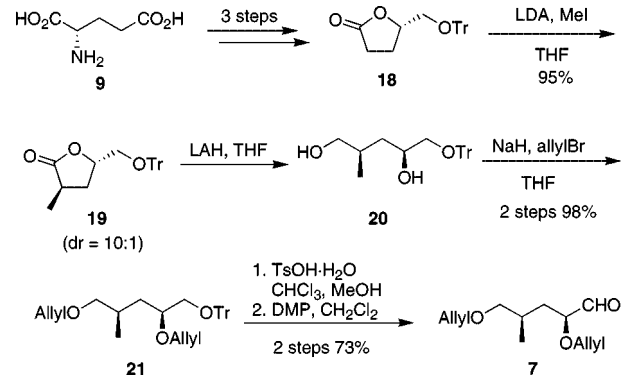
of bromide **3** to aldehyde **4** and following spiroketalization. Fragment **3** would be synthesized from commercially available chiral synthons **5** and **6** through asymmetric dihydroxylation. Fragment **4** would be prepared through the addition of fragment **8** to fragment **7**. Fragments **7** and **8** are synthesized through diastereoselective methylation from an L-glutamic acid (**9**) and an enantioselective alcoholysis of **10** using lipase, respectively.

Synthesis of the fragment **3** containing four chiral centers began with a commercially available chiral synthon **5** (Scheme 2). Protection of the hydroxyl group of **5** and half-reduction gave known aldehyde **11**.[6] Subsequent formation of a carbon−carbon triple bond by the treatment of **11** with the Ohira−Bestmann reagent **12**[7] gave alkyne **13** in 61% yield over the three steps. Subsequent treatment of **13** with a Schwalts reagent (Cp_2ZrHCl) and iodine provided (*E*)-iodoalkene **14** in 89% yield. The coupling reaction of two fragments **14** and **15**, prepared from **6** by the protection of a hydroxyl group, was examined. The S_N2 reaction of the anion, derived from **14**, with a bromide **15** did not proceed due to steric reasons around the carbon atom bearing a bromine atom on **15**. The coupling reaction of **14** with **15** was achieved by employing the Suzuki−Miyaura coupling reaction[8] after converting **15** to an organoboron reagent, and **16** was obtained in excellent yield (96%). The Sharpless asymmetric dihydroxylation of **16** for the creation of two

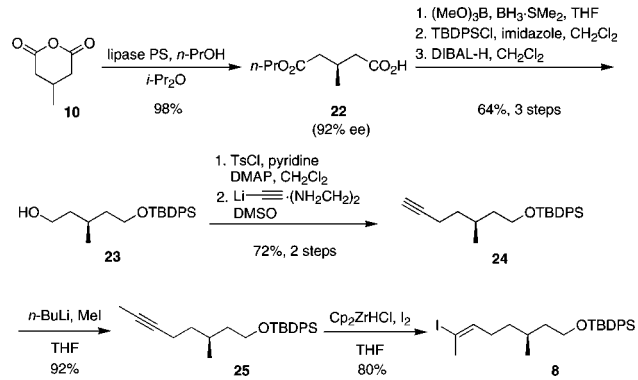
Scheme 2. Synthesis of Fragment **3**



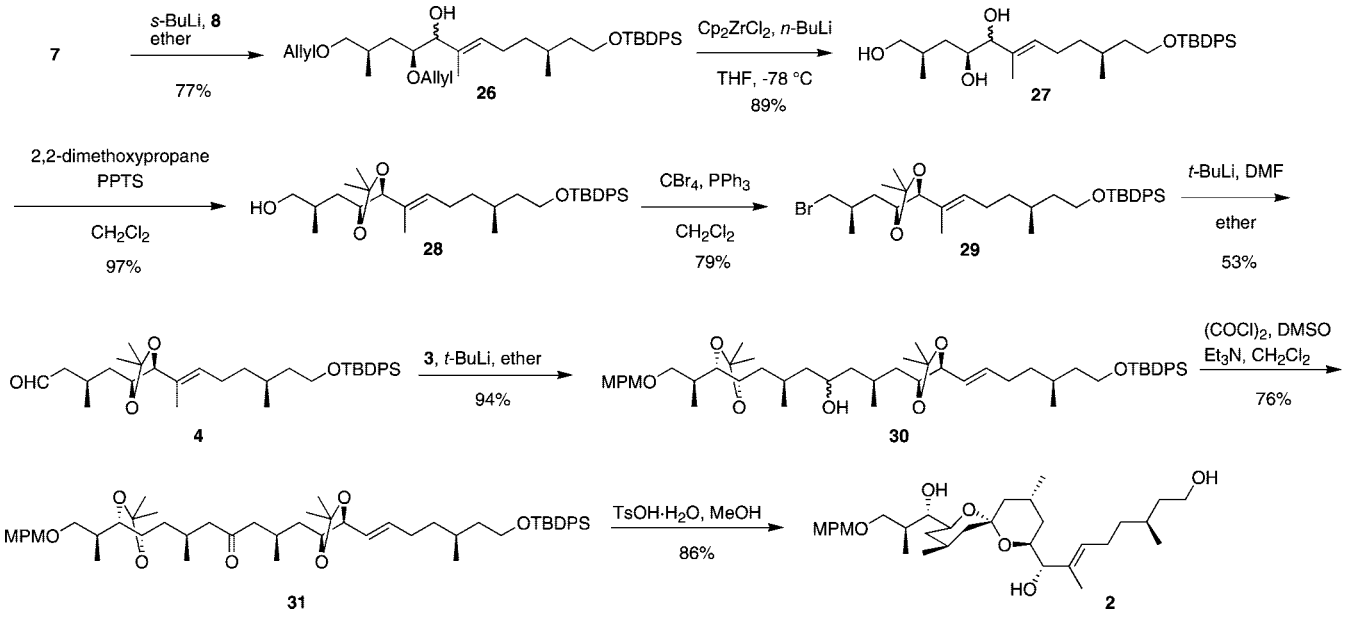
Scheme 3. Synthesis of Fragment **7**



Scheme 4. Synthesis of Fragment **8**



Scheme 5. Synthesis of Subunit **2** through Coupling Reactions of Three Fragments, **7**, **8**, and **3**



chiral centers and following protection of the resulting diol moiety gave **17** in 57% yield for the two steps as a single isomer. After deprotection of the TBDPS group of **17** and bromination of the resulting hydroxy group, fragment **3** was obtained (93% yield for the two steps).

Fragment **7** possessing two chiral centers was prepared from L-glutamic acid (**9**) as shown in Scheme 3. Known compound **18** was prepared from **9** through a three-step sequence according to the literature procedure.[9] Stereoselective methylation of **18** with LDA and iodomethane gave **19** in 95% yield (dr = 10:1).[10] The reduction of **19** to afford the known diol **20**[11] and both hydroxyl groups of **20** were converted to allyl ethers to obtain compound **21** (98% yield for the two steps). Deprotection of the trityl group of **21**, followed by oxidation of the hydroxyl group, gave fragment **7** (73% yield for the two steps).

The synthesis of fragment **8** is shown in Scheme 4. Compound **22** was prepared from 3-methylglutaric anhydride (**10**) by enantioselective alcoholysis using lipase PS with *n*-PrOH according to the literature procedure (98% yield, 92% ee).[12] Reduction of the carboxylic acid moiety of **22** with a borane−dimethylsulfide complex, protection of the hydroxyl group, and reduction of the isopropyl ester with DIBAL-H gave **23** (64% for the three steps). The hydroxyl group of **23** was tosylated, and the following introduction of the acetylene unit by the addition of the lithium acetylide−ethylenediamine complex gave **24** in 72% yield over the two steps. Introduction of the methyl group to terminal alkyne (92%) and site- and stereoselective iodination of **25** using a Schwartz reagent and iodine produced fragment **8** in 80% yield.

Fragment **4** was synthesized through the coupling reaction of fragments **7** with **8** (Scheme 5). The addition reaction of a vinyllithium derivative, which was prepared from **8** by treatment with an *s*-BuLi, with aldehyde **7** proceeded to give **26** in 77% yield as a diastereomeric mixture (1:1). Although the addition reaction of the analogues of fragment **7** having other protecting groups (MPM or MOM) was examined, the diastereoselectivity of the reaction did not improve. At this stage, separation of the diastereomer was not successful. Therefore, **26** was converted to **28** as a diastereomeric mixture. Deprotection of allyl groups of **26** using a reaction

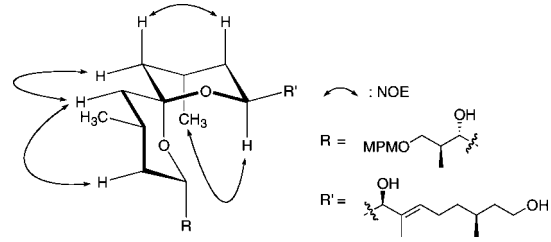


Figure 1. NOE correlations of the spiroketal moiety of **2**.

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of a zirconocene equivalent[13] and selective protection of a 1,2-diol moiety using 2,2-dimethoxypropane gave **28** in 86% yield for two steps. After separation of diastereomers, the desired diastereomer of **28**[14] was converted to a bromide **29** in 79% yield. One carbon elongation was examined by the formylation of **29** using a *t*-BuLi with DMF, and fragment **4** was obtained in 53% yield. The coupling reaction of fragments **3** and **4** was achieved as follows (Scheme 5). Lithiation of **3** by the reaction of **3** with *t*-BuLi and an addition of the resultant anion to aldehyde **4** gave compound **30** in excellent yield (94%). The hydroxyl group of **30** was oxidized by Swern oxidation to give **31** in 76% yield. The formation of a spiroketal moiety was achieved during the deprotection of two acetonide groups by treating **31** with TsOH in methanol, and subunit **2** was obtained in 86% yield as a single isomer. The relative stereochemistry of the spiroketal moiety of subunit **2** was determined by NOESY spectra: NOE correlations of **2** are shown in Figure 1.

In conclusion, we have described a convergent synthesis of the C9−C28 subunit of didemnaketal B. The present strategy required only 16 steps even in the longest linear sequence.

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Supporting Information Available: Detailed experimental procedure and characterization data for new compounds and ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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